CASE REPORT

Chinese Siblings with Prader-Willi Syndrome Inherited from Their Paternal Grandmother

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Background: Prader-Willi syndrome (PWS) is a complex neurobehavioral disorder caused by failure of expression of paternally inherited genes in the *PWS* region of chromosome 15. **Case characteristics**: Two siblings who both met the inclusion criteria for clinical diagnosis of PWS during neonatal period. **Outcome**: Molecular genetic analysis demonstrated a 417-kb microdeletion within the 15q11.2 region inherited from siblings' paternal grandmother, involving key genes of *PWS*, except for *UBE3A*, which may explain why their father and paternal grandmother had a normal phenotype. **Conclusion**: The findings may be helpful for better understanding of the underlying mechanism of this rare imprinting defect.

Keywords: *Microdeletion, Mode of inheritance, Molecular genetic* analysis.

Prader-Willi syndrome (PWS; MIM 176270) is a genomic imprinting disorder – 70% of individuals with PWS have a *de novo* paternal microdeletion of the chromosome 15q11.2-q13 region (so-called PWS/AS region), namely paternal deletion type. About 25% of individuals have maternal disomy 15 of chromosome 15q11.2-q13 region, namely uniparental disomy (UPD) type. Less than 3% have defects in the genomic imprinting due to microdeletion or epimutation [1]. On very rare occasions, chromosomal translocations or rearrangements of the 15q11.2-q13 region have been reported [2]. The epigenetic and genomic changes causing PWS entirely lead to a loss of the expression of the paternally expressed genes on 15q11.2-q13 region because the maternal contribution for these genes has been programmed by epigenetic factors to be silenced [3]. Conversely, loss of the expression of preferentially maternally expressed *UBE3A* in this region by several possible mechanisms may lead to Angelman syndrome [4]. We report two siblings with PWS due to shorter microdeletions inherited from their paternal grandmother.

Case Report

The proband was a Chinese 20-day-old male infant born to non-consanguineous parents (parents' age 28 years) at gestational age of 40 weeks by caesarean section. During pregnancy, mother perceived decreased intrauterine movement. He had birth weight of 3.15 kg and length of 50 cm. Hypotonia, weak cry, weak suck, and feeding problems were noted after birth. Physical examination showed lethargy, abnormal facies (narrow face, micrognathia, high-arched palate, a thin upper lip with a down-turned mouth), generalized hypopigmen-tation, brown hairs, small genitalia, cryptorchidism, and poor reflexes. Biochemical analyses, including blood electrolytes, liver and renal function tests, thyroid function test, and serological testing for perinatal infections were normal. The parents were healthy, with normal intelligence, except that the mother had hepatitis B virus (HBV) infection with normal liver function.

His older sister was vaginally delivered at 41 weeks of gestation, and had died at 4 day of age. She was hypotonic, never cried, and had a weak suck. She also had lethargy, abnormal facies (micrognathia, a thin upper lip with a down-turned mouth), brown hairs, external genital deformity, strephexopodia, and poor reflexes. The pedigree of the proband's family and pictures of the siblings are shown in ***Fig***. **1** and **2**.

As two siblings were affected, hereditary disease was suspected. Karyotyping (450-550 bands) was done for the proband, his sister, and his parents in a local hospital by Guangzhou Kingmed Diagnostics Group Co. Ltd. (Guangzhou, China). A total of 50 metaphase cells were analyzed. The karyotypes of the proband, and his father were normal, while the karyotype of his mother was 46, XX 9qh+.

Single nucleotide polymorphism (SNP) based chromosomal microarray analysis was performed by using the Infinium OmniZhongHua-8 kit (San Diego,

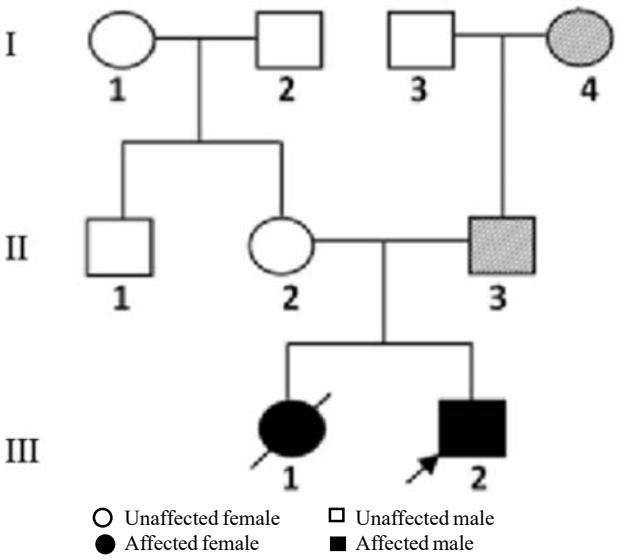

FIG. 1 *The three-generation pedigree of the affected family.*

CA, USA) according to the manufacturer's instructions. The KaryoStudio software (Illumina, Inc., San Diego, CA, USA), and Database of Genomic Variants (DGV) were utilized to detect and analyze copy number variations (CNVs). A 417-kb microdeletion in chromosome 15q11.2 [Hg19 arr15q11.2(24 963 375-25 380 656)×1] was found for the proband and his father. This region involved the imprinting center of PWS/AS, SNURF-SNRPN and SNORD107, SNORD64, SNORD 109A, SNORD116, SNORD115, and SNORD109B. A 206-kb microdeletion in chromosome 4p16.1 [arr4p16.1(8 218 420-8 424 831)×1] and a 149-kb microduplication in chromosome 16p13.2 [arr16p13.2(8 798 528-8 948 473)×3] were found for his mother.

The analysis was subsequently followed by methylation sensitive multiplex ligation-dependent probe amplification (MS-MLPA) of the proband, his father, and paternal grandmother to confirm the diagnosis of PWS; and explore the origin of variations using SALSA MS-MLPA ME028-B2 Prader Willi/Angelman kit (MRC Holland, Amsterdam, The Netherlands). This kit contains 46 probes, 32 of which are specific for sequences in or close to the PWS/AS critical region on 15q11.2-q13 which can be used to detect CNVs in this region. A heterozygous microdeletion containing the imprinting center ranging from SNRPN intron u1 through the SNRPN locus and SNORD 107 to SNORD 109B snoRNA cluster located at 15q11.2 was found on the proband, his father, and his grandmother. DNA methylation abnormalities were noted as well, including 100% methylation for the proband, and 0% methylation for his father and grandmother.

FIG. 2 *The clinical pictures of (a) proband, and (b) his sister. Both showed abnormal facies (narrow face, micrognathia, almond eye, a thin upper lip with a down-turned mouth), generalized hypopigmentation, and brown hairs.*

The proband, his father, and his grandmother all underwent linkage analysis, and the analysis showed that the alleles of SNRPN-12N, -13N, -14N, and -15N were dropped out.

These allelic sites were used for the preimplantation genetic diagnosis (PGD) based on linkage analysis. It was revealed that 5 of the 12 blastocysts were normal and the mother was ready to receive the implantation.

DISCUSSION

PWS is an imprinted neurobehavioral condition, influencing several organs, and mainly occurs due to the absence of expression of a cluster of paternally expressed genes located at 15q11-q13. PWS is usually sporadic; however, in some families, an epimutation or incomplete processing of imprinting in germ cell may negatively influence the process, originating from father or from microdeletion of the DNA imprinting center. The mentioned microdeletion defect has been reported in about 15% of individuals with PWS due to imprinting defect (ID) [5]; although, recent studies have indicated a possible higher rate of microdeletion in the imprinting center (IC) [6]. This microdeletion can be derived from the paternal grandmother through the father, and may lead to birth of another child with PWS, and its risk may reach 50%. However, if microdeletion only passes through the maternal line, no phenotypic effect may occur, while her sons may be at a 50% risk of having children with PWS, and her daughters' sons may also be at risk of having children with PWS [7]. In the majority of reported cases, the IC deletion was familial, and in contrast, none of the patients with a non-IC deletion have an affected sibling [8].

The proband and his older sister both met major and minor criteria for clinical diagnosis of PWS presented by Holm, *et al*. [9,10], and the diagnostic scores were both equal to 5.5. Hartin, *et al*. [7] reported the clinical and genetic findings in three adult siblings with PWS caused by a microdeletion in the chromosome 15 imprinting center inherited from an unaffected father that controls the activity of genes in the 15q11-q13 region. They demonstrated that the PWS siblings' mother displayed a normal copy number for the same probes, indicating that she did not carry a microdeletion in the PWS imprinting center [10]. The maternal imprint could not be erased in the paternal germline in those PWS cases with imprinting center defects.

In conclusion, the wide variety of phenotypes that involve multiple organ systems match with the genetic complexity of the PWS chromosomal region, with multiple imprinted genes, gene duplication and CNVs, alternative splice variants, and the mechanisms of imprinting. Reporting of families with more than one affected individuals with PWS, which were not related to translocation or inversion of chromosome 15, can be helpful to identify the genetic defect within the imprinting center.

Contributors: Dai YL, Huang K: diagnosed and managed the case, and drafted the initial manuscript; Dong GP, Zou CC supervised the patient care and reviewed and revised the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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